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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/728,067	12/03/2003	Kenneth F. Buechler	071949-5604	7956

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EXAMINER	
JUNG, UNSU	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 12/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/728,067	BUECHLER ET AL.	
	Examiner	Art Unit	
	Unsu Jung	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-44* is/are pending in the application.

4a) Of the above claim(s) *1-31* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *32-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 December 2003* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

2/27/04, 1/24/05, 4/7/05, 6/27/05, 9/6/05, 2/21/06, 4/25/06, and 8/16/06

DETAILED ACTION

1. Claims 1-44 are pending and claims 32-44 are under consideration for their merits.

Election/Restrictions

2. Applicant's election of Group II (claims 32-44) and species election of sex for list I (risk factors) and markers related to myocardial injury markers for list II (subject-derived markers) in the reply filed on October 5, 2006 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

It has been acknowledged that a monocyte chemoattractant protein-1 (MCP-1) has been deleted from List II of the subject-derived markers of Office Action dated September 11, 2006 (p8) because MCP-1 is a requirement of all the Group II claims as noted by the Applicant on October 5, 2006.

Sequence Compliance

3. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To

Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

Applicants must file the items indicated below within the time period set forth in this Office Action to avoid abandonment under 35 U.S.C. 133 (extensions of time may be obtained under the provisions of 35 CFR 1.136(a)). The amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 35 CFR 1.821-1.825 for the following reasons(s):

- This application clearly fails to comply with the requirements of 37 CFR 1.821-1.825. Applicant's attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990). If the effective filing date is on or after July 1, 1998, see the final rule making notice published at 63 FR 29620 (June 1, 1998) and 1211 OG 82 (June 23, 1998).
- A paper copy of the "Sequence Listing" for sequences on p24 (SEQ ID NO:1 and SEQ ID NO:2) of the specification, as well as an amendment specifically directing its entry into the application has not been submitted.
- A copy of "Sequence Listing" for sequences on p24 (SEQ ID NO:1 and SEQ ID NO:2) of the specification in computer readable form has not been submitted as required by 37 CFR 1.821(e).
- A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, has not been submitted as required by 37 CFR 1.821(e) or 1.821(f) or 1.821 (g) or 1.825(b) or 1.825(d).

Applicants must provide:

- A paper copy of the "Sequence Listing", as well as an amendment specifically directing its entry into the application
- A copy of "Sequence Listing" in computer readable form as required by 37 CFR 1.821(e)
- A statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821 (g) or 1.825(b) or 1.825(d)
- Sequence identifiers and sequence ID numbers for the sequences listed throughout the specification

Applicant is required to thoroughly review the specification and comply with all sequence rules. Where the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with 37 CFR 1.821(c), reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence is also embedded in the text of the description or claims of the patent application.

Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

If a complete response has not been submitted by the time the shortened statutory period for response set THREE MONTHS from the mailing date of this action has expired, this application will become abandoned unless applicant corrects the deficiency and obtains an extension of time under 37 C.F.R. 1.136. In no case may an applicant extend the period for response beyond the six-month statutory period.

Information Disclosure Statement

4. The following references of the information disclosure statement filed on February 14, 2003 should be corrected as indicated on the information disclosure statement:

- Application number, filing date, and attorney docket number on each page has been corrected to reflect current application (10/728,067) information rather than the parent application (10/330,696) information;
- C13 (p3 of 27): volume number (9) of the journal is missing;
- C26 and C27 (p4 of 27): journal information (journal name, volume, pages, and year) should be corrected;
- C62 (p6 of 27): volume number should be corrected to "114B";
- C66 (p7 of 27): the word "center" should be corrected to "cancer";
- C73 (p7 of 27): the last name of the author should be corrected to "Portales";
- C98 (p9 of 27): the volume number should be corrected to "78";
- C103 (p10 of 27): quotation mark is missing from the title;
- C124 (p11 of 27): a comma following the word "Clin." should be deleted;
- C149 (p13 of 27): quotation mark is missing from the title;
- C179 (p15 of 27): page number "641" should be corrected to "647";
- C185 (p16 of 27): the title should be corrected to "Cerebral ischemia produces laddered DNA fragments distinct from cardiac ischemia and archetypal apoptosis";

- C204 (p17 of 27): the journal name should be corrected to "J. Biol. Chem.";
- C261 (p21 of 27): the volume number should be corrected to 17;
- C281 (p23 of 27): the publication year should be corrected to "1985";
- C299 (p25 of 27): the editor's name (Burtis et al.) should be included and the page number should be corrected to "485-507";
- C314 (p26 of 27): the title should be corrected to "Serum measurements of eosinophil cationic protein (ECP) in bronchial asthma"
- C327 (p27 of 27): the page number should be corrected to "170-6"; and
- C328 (p27 of 27): the page number should be corrected to "285-297."

5. The second page of information disclosure statement filed on February 21, 2006 fails to comply with 37 CFR 1.98(a)(1), which requires the following: (1) a list of all patents, publications, applications, or other information submitted for consideration by the Office; (2) U.S. patents and U.S. patent application publications listed in a section separately from citations of other documents; (3) the application number of the application in which the information disclosure statement is being submitted on each page of the list; (4) a column that provides a blank space next to each document to be considered, for the examiner's initials; and (5) a heading that clearly indicates that the list is an information disclosure statement. The information disclosure statement has been placed in the application file, but the information referred to therein has not been considered.

Drawings

6. The drawings are objected to because Fig. 2 is missing lines for x- and y-axis. Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Specification

7. Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly

those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

Extensive mechanical and design details of apparatus should not be given.

The current Abstract fails to include a concise statement of the claimed invention, which is a method of diagnosing atherosclerosis in a subject, as the Abstract only includes a method of diagnosing myocardial injury, but not atherosclerosis. Therefore, the current Abstract fails to provide a concise statement of the technical disclosure of the patent and does not include that which is new in the art to which the invention pertains. See MPEP § 608.01(b).

8. The use of the trademarks ELECSYS™ (p73, paragraph [0224], line 3) and AXSYM® (p73, paragraph [0224], line 3) has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejections - 35 USC § 112, First Paragraph

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Written Description

Claims 32-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, as of the filing date of the application, of the specific subject matter later claimed. The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention." MPEP § 2163.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. The MPEP states that:

"The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction

to practice...or by disclosure of relevant, identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus" MPEP § 2163.

The MPEP does state that for a generic claim, the genus can be adequately described if the disclosure presents a sufficient number of representative species that encompass the genus. MPEP § 2163. If the genus has a substantial variance, the disclosure must describe a sufficient variety of species to reflect the variation within that genus. See MPEP § 2163. Although the MPEP does not define what constitutes a sufficient number of representative species, the courts have indicated what do not constitute a representative number of species to adequately describe a broad generic. In *Gostelli*, the courts determined that the disclosures of two chemical compounds within a subgenus did not describe that subgenus. In re Gostelli 872, F.2d at 1012, 10 USPQ2d at 1618.

In the instant case, the claims are drawn to a method of diagnosing atherosclerosis in a subject, comprising the steps of determining a presence or amount of monocyte chemoattractant protein-1 (MCP-1) or a marker related thereto in a sample from the subject and correlating the presence or amount of MCP-1 to the presence or absence of atherosclerosis in the subject. The invention is further drawn to assaying for additional subject-derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis.

The claims are not limited as to the number of markers, since claim 34 recites "determining the presence or amount of MCP-1 or a marker related thereto." The

current specification defines the term "related marker" as being one or more fragments of a particular marker or its biosynthetic parent that may be detected as a surrogate for the marker itself or as independent markers (p24, paragraph [0068]). Additionally, related markers may be the result of covalent modification of the parent marker, for example by oxidation of methionine residues, ubiquitination, etc (p24, paragraph [0068]). The currently recited claims are drawn to determining the presence or amount of MCP-1 or a marker related thereto. There is no description in the specification disclosing what the fragments and modifications of MCP-1 are.

As disclosed in the current specification (p23, paragraph [0064]), MCP-1 has been implicated in the pathogenesis of a variety of diseases that involve monocyte infiltration, including psoriasis, rheumatoid arthritis, and atherosclerosis. The normal concentration of MCP-1 in plasma is <0.1 ng/ml. The plasma concentration of MCP-1 is elevated in patients with acute myocardial infarction (AMI), and may be elevated in the plasma of patients with unstable angina, but no elevations have been associated with stable angina (Soejima et al., *J. Am. Coll. Cardiol.* 1999, Vol. 34, pp983-988; Nishiyama et al., *Jpn. Circ. J.*, 1998, Vol. 62, pp710-712; Matsumori et al., *J. Mol. Cell. Cardiol.*, 1997, Vol. 29, pp419-423). The current specification (p23, paragraph [0065]) further discloses that elevations of the serum concentration of MCP-1 are associated with various conditions associated with inflammation, including alcoholic liver disease, interstitial lung disease, sepsis, and systemic lupus erythematosus (Fisher et al., *Gut*, 1999, Vol. 45, pp416-420; Suga et al., *Eur. Respir. J.*, 1999, Vol. 14, pp376-382; Bossink et al., *Blood*, 1995, Vol. 86, pp3841-3847; Kaneko et al. *J. Rheumatol.*, 1999,

Vol. 26, pp568-573). Further, MCP-1 is a specific marker of the presence of a pro-inflammatory condition that involves monocyte migration.

The current state of the art (Vasan, *Circulation*, 2006, Vol. 113, pp2335-2362) of cardiovascular disease teaches that biomarkers are used to identify high-risk individuals to diagnose disease conditions promptly and accurately (p2335). Vasan teaches that biomarkers can be used as indicators of disease trait (risk factor or risk marker) and diagnostic markers (recognizing overt disease, p2335, right column, first paragraph). For diagnostic markers, features such as high sensitivity, specificity, and predictive values are important (p2336, left column and Table 2). However, MCP-1 does not possess one of the important features of diagnostic markers as MCP-1 has been implicated in the pathogenesis of a variety of diseases that involve monocyte infiltration, including psoriasis, rheumatoid arthritis, and atherosclerosis and elevations of the serum concentration of MCP-1 are associated with inflammation, including alcoholic liver disease, interstitial lung disease, sepsis, and systemic lupus erythematosus. Consequently, MCP-1 lacks specificity as it is associated with variety of diseases other than atherosclerosis and therefore the presence/absence of atherosclerosis would not be predicted by determining the presence/amount of MCP-1 alone, which is further supported by Takebayashi et al. (*J. Diabetes and Its Complications*, 2006, Vol. 20, pp98-104), which teaches that MCP-1 may not be a marker for atherosclerosis in non-obese Type 2 diabetic patients (Abstract). Therefore, MCP-1 does not satisfy features of diagnostic markers for atherosclerosis as MCP-1 is an indicator of variety of diseases

other than atherosclerosis as discussed above and the presence or amount of MCP-1 alone is not capable of specifically diagnosing atherosclerosis in a subject.

The current specification (Fig. 2 and p83, paragraph [0254]) shows the association of MCP-1 to subclinical atherosclerosis in 2733 patients who had an EBCT scan. Of these, 581 patients had evidence of subclinical atherosclerosis defined as a coronary calcification score ≥ 10. Therefore, the example in the current specification fails to demonstrate that MCP-1 alone can be used as a specific diagnostic marker of atherosclerosis since only 581 patients were confirmed as having an evidence of subclinical atherosclerosis determined using coronary calcification score among 2733 patients, who showed subclinical atherosclerosis as measured by the presence/amount of MCP-1.

Furthermore, The claims are not limited as to the number of markers, since claims 40 and 41 recite "determining the presence or amount of one or more subject-derived markers" and would encompass, for example 216 different subject-derived markers as disclosed in the current specification (pp58-62) as well as those markers not listed in the specification. Further, claim 41 is directed to assaying for additional subject-derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis and the currently recited claims would include list of markers disclosed in the current specification (216 markers, pp58-62) as well as those specific markers not listed in the specification. The specification discloses that MCP-1 and optionally one or more of these additional markers can be used as part of diagnostic panel, which may comprise

2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, or more of individual markers, wherein at least one of the individual markers is MCP-1 (pp13-14, paragraph [0039]), which means that there are at least more than $2x10^{216}$ different panels that can be made up from various possible marker combinations, i.e. $2x10^{216}$ different assays measuring different sets of markers in order to carry out the claimed invention. However, the specification fails to provide specific panel of MCP-1 and additional marker combinations, which can be used to diagnose atherosclerosis in a subject. Therefore, the specification fails to teach the skilled artisans that the inventor(s) had possession, as of the filing date of the application, of the specific subject matter later claimed.

Since each marker represents a unique polypeptide of distinct structure and functional properties, methods that involve the detection of different markers or different sets of markers would differ substantially. For example, any given marker would not be capable of diagnosing atherosclerosis. In light of substantial variance among the genus of methods claimed, one skilled in the art would not understand the inventor(s) to have possession of the entire genus based on the limited methods described.

Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of claims and does not reasonably convey to one skilled in the relevant art that the inventor(s), at the time of the application was filed, had possession of the entire genus of the claimed invention.

11. Enablement

Claims 32-44 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The nature of the invention is drawn to a method of diagnosing atherosclerosis in a subject, comprising the steps of determining a presence or amount of monocyte chemoattractant protein-1 (MCP-1) or a marker related thereto in a sample from the subject and correlating the presence or amount of MCP-1 to the presence or absence of atherosclerosis in the subject. The invention is further drawn to assaying for additional subject-derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis.

As disclosed in the current specification (p23, paragraph [0064]), MCP-1 has been implicated in the pathogenesis of a variety of diseases that involve monocyte infiltration, including psoriasis, rheumatoid arthritis, and atherosclerosis. The normal concentration of MCP-1 in plasma is <0.1 ng/ml. The plasma concentration of MCP-1 is elevated in patients with acute myocardial infarction (AMI), and may be elevated in the plasma of patients with unstable angina, but no elevations have been associated with stable angina (Soejima et al., *J. Am. Coll. Cardiol.* 1999, Vol. 34, pp983-988; Nishiyama et al., *Jpn. Circ. J.*, 1998, Vol. 62, pp710-712; Matsumori et al., *J. Mol. Cell. Cardiol.*, 1997, Vol. 29, pp419-423). The current specification (p23, paragraph [0065]) further

discloses that elevations of the serum concentration of MCP-1 are associated with various conditions associated with inflammation, including alcoholic liver disease, interstitial lung disease, sepsis, and systemic lupus erythematosus (Fisher et al., *Gut*, 1999, Vol. 45, pp416-420; Suga et al., *Eur. Respir. J.*, 1999, Vol. 14, pp376-382; Bossink et al., *Blood*, 1995, Vol. 86, pp3841-3847; Kaneko et al. *J. Rheumatol.*, 1999, Vol. 26, pp568-573). Further, MCP-1 is a specific marker of the presence of a pro-inflammatory condition that involves monocyte migration.

The current state of the art (Vasan, *Circulation*, 2006, Vol. 113, pp2335-2362) of cardiovascular disease teaches that biomarkers are used to identify high-risk individuals to diagnose disease conditions promptly and accurately (p2335). Vasan teaches that biomarkers can be used as indicators of disease trait (risk factor or risk marker) and diagnostic markers (recognizing overt disease, p2335, right column, first paragraph). For diagnostic markers, features such as high sensitivity, specificity, and predictive values are important (p2336, left column and Table 2). However, MCP-1 does not possess one of the important features of diagnostic markers as MCP-1 has been implicated in the pathogenesis of a variety of diseases that involve monocyte infiltration, including psoriasis, rheumatoid arthritis, and atherosclerosis and elevations of the serum concentration of MCP-1 are associated with inflammation, including alcoholic liver disease, interstitial lung disease, sepsis, and systemic lupus erythematosus. Consequently, MCP-1 lacks specificity as it is associated with variety of diseases other than atherosclerosis and therefore the presence/absence of atherosclerosis would not be predicted by determining the presence/amount of MCP-1 alone, which is further

supported by Takebayashi et al. (*J. Diabetes and Its Complications*, 2006, Vol. 20, pp98-104), which teaches that MCP-1 may not be a marker for atherosclerosis in non-obese Type 2 diabetic patients (Abstract). Therefore, MCP-1 does not satisfy features of diagnostic markers for atherosclerosis as MCP-1 is an indicator of variety of diseases other than atherosclerosis as discussed above and the presence or amount of MCP-1 alone is not capable of specifically diagnosing atherosclerosis in a subject.

The current specification (Fig. 2 and p83, paragraph [0254]) shows the association of MCP-1 to subclinical atherosclerosis in 2733 patients who had an EBCT scan. Of these, 581 patients had evidence of subclinical atherosclerosis defined as a coronary calcification score ≥ 10. Therefore, the example in the current specification fails to demonstrate that MCP-1 alone can be used as a specific diagnostic marker of atherosclerosis since only 581 patients were confirmed as having an evidence of subclinical atherosclerosis determined using coronary calcification score among 2733 patients, who showed subclinical atherosclerosis as measured by the presence/amount of MCP-1.

The claims are directed to assaying for additional subject-derived specific markers of myocardial injury, neural tissue injury, blood pressure regulation, coagulation, hemostasis, inflammation, and apoptosis and the currently recited claims (40 and 41) would include list of markers disclosed in the current specification (216 markers, pp58-62) as well as those markers not listed in the specification. The specification discloses that MCP-1 and optionally one or more of these additional markers can be used as part of diagnostic panel, which may comprise 2, 3, 4, 5, 6, 7, 8,

9, 10, 15, 20, or more of individual markers, wherein at least one of the individual markers is MCP-1 (pp13-14, paragraph [0039]), which means that there are at least more than $2x10^{216}$ different panels that can be made up from various possible marker combinations, i.e. $2x10^{216}$ different assays measuring different sets of markers in order to carry out the claimed invention. However, the specification fails to provide specific panel of MCP-1 and additional marker combinations, which can be used to diagnose atherosclerosis in a subject. Therefore, the specification fails to teach the skilled artisans how to detect all subject-derived markers in all sample types and how to use this information can be used to diagnose atherosclerosis in a subject.

The courts have stated that "tossing out the mere germ of an idea does not constitute enabling disclosure." Genentech, 108, F.3d at 1366 (quoting Brenner v. Manson, 383 U.S. 519, 536 (1996) (stating, in context of the utility requirement, that a "patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"). "[R]easonable detail must be provided in order to enable members of the public to understand and carry out the invention." Id. The courts have further stated that "if mere plausibility were the test for enablement under section 112, applicants could obtain patent rights to "inventions" consisting of little more than respectable guesses as to the likelihood of their success. When one of the guesses are later proved true, the "inventor" would be rewarded the spoils instead of the party who demonstrated that the method actually worked. That scenario is not consistent with the statutory requirement that the inventor enable an invention rather than merely proposing

unproved hypothesis." Rasmusson v. SmithKline Beecham Corp., 75 USPQ2d 1297 (CA FC 2005).

In the instant case, such reasonable detail is lacking. The specification lists a large number of different subject-derived markers, and suggests that one skilled in the art would use information relating to the presence or amount of various different combinations of these markers in order to diagnose atherosclerosis in a subject. However, the specification fails to identify which specific panel of markers should be measured in order to diagnose atherosclerosis in a subject. The specification further fails to disclose what levels of each marker would be indicative of atherosclerosis in a subject.

Although the specification outlines art-recognized methodology that can be used in conducting investigational studies to test and validate biomarkers for various diagnostic purposes, such a general roadmap amounts to an invitation to conduct further research, rather than a specific direction required to enable one of ordinary skill in the art to understand and carry out the invention. Hence, this general outline for how to test and validate different sets of biomarkers for diagnosing atherosclerosis in a subject fails to constitute an enabling disclosure in light of complexity, unpredictability and laborious nature of biomarker validation (discussed further below) and furthermore fails to provide one skilled in the art with any reasonable expectation of success in using any particular combination of markers to diagnose atherosclerosis in a subject. The specification sets forth a research plan, not an invention to be practiced.

As a result, in order to carry out the claimed invention, one skilled in the art would first need to determine whether any given set of markers claimed could in fact be used diagnostically, i.e. whether the markers claimed are actually valid biomarkers of the atherosclerosis in a subject, which would mean conducting large-scale clinical investigations in order to compare the levels of each marker in both control and disease patients, and to determine whether statistically significant changes in marker levels are observed and correlated with current gold-standard clinical diagnostic methods. This type of clinical investigations would need to be done for each type of cardiovascular disorder. In addition, one skilled in the art would also need to determine what levels or ranges of levels of each of the markers would be indicative of atherosclerosis in a subject. Such investigative research to test and validate all of the biomarkers for use in diagnosing atherosclerosis in a subject is not of a routine nature and clearly represents an undue burden.

For example, Bast, Jr. et al. (*Clinical Cancer Research*, 2005, Vol. 11, pp6103-6108) point to the "lengthy process" of assay development and validation and note that many markers that correlate with disease statistically may not prove to be useful clinically (p6105, right column). Similarly, LaBaer et al. (*Journal of Proteome Research*, 2005, Vol. 4, pp1053-1059) teaches that crucial validation steps are needed to demonstrate that an identified biomarker is a reliable predictor and also that the process of converting such a biomarker into a practical clinical test is even more daunting (p1053, paragraph bridging the left and right columns). In addition, Baker (*Nature*

Biotechnology, 2005, Vol. 23, pp297-304) speaks to the unpredictability involved in clinically applying biomarkers (p298, *Walking on Thin Ice*).

In summary, the specification fails to teach that MCP-1 alone can be used to diagnose atherosclerosis in a subject and the specification lists a large number of possible subject-derived markers and suggests the use of various combinations of the subject-derived markers for diagnosing atherosclerosis in a subject. However, the specification lacks clinical data validating the various biomarker combinations corresponding to the atherosclerosis in a subject, and fails to disclose specific guidance regarding, which specific panels of markers are to be used to diagnose atherosclerosis in a subject and what levels would be indicative of atherosclerosis in a subject. Taken together with the breadth of the claims, lack of examples, unpredictability associated with validation of biomarkers for clinical use, and current state of the art, which teaches that MCP-1 may be not a marker for atherosclerosis, the specification fails to teach the skilled artisan how to make and use the claimed invention in its full scope without further undue experimentation.

Claim Rejections - 35 USC § 112, Second Paragraph

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 32-44 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

14. Claim 32 recites the limitation "the presence or amount of monocyte chemoattractant protein-1" in line 2. There is insufficient antecedent basis for this limitation in the claim.

15. In claim 32, the phrase "correlating the presence of amount of monocyte chemoattractant protein-1 to the presence or absence of atherosclerosis in the subject" is vague and indefinite. It is unclear how the presence of amount of monocyte chemoattractant protein-1 can determine the to the presence or absence of atherosclerosis in the subject.

16. In claim 33, the term "a marker related thereto" in lines 2, 4, and 6 is vague and indefinite. It is unclear whether or not the term "a marker related thereto" in lines 2, 4, and 6 of claim 33 is referring to "a marker related thereto" in line 3 of claim 32. For the purpose of examination, the term "a marker related thereto" in lines 2, 4, and 6 of claim 33 has been interpreted as referring to "a marker related thereto" in line 3 of claim 32.

17. In claim 33, the term "a concentration of monocyte chemoattractant protein-1 or a marker related thereto" in lines 3-4 and 5-6 is vague and indefinite. It is unclear whether

or not the term "a concentration of monocyte chemoattractant protein-1 or a marker related thereto" in lines 3-4 and 5-6 is referring to "the concentration of monocyte chemoattractant protein-1 or a marker related thereto" in lines 2-3. For the purpose of examination, the term "a concentration of monocyte chemoattractant protein-1 or a marker related thereto" in lines 3-4 and 5-6 has been interpreted as referring to "the concentration of monocyte chemoattractant protein-1 or a marker related thereto" in lines 2-3.

18. In claim 33, the step of "determining the concentration of monocyte chemoattractant protein-1 or a marker related thereto in said sample" is vague and indefinite. It is unclear whether or not the step of determining the concentration of monocyte chemoattractant protein-1 or a marker related thereto in said sample is a specific step of "determining the presence or absence or monocyte chemoattractant protein-1 or a marker related thereto in a sample from said subject" in claim 32. For the purpose of examination, the step of "determining the concentration of monocyte chemoattractant protein-1 or a marker related thereto in said sample" in claim 33 has been interpreted as being the specific of "determining the presence or absence or monocyte chemoattractant protein-1 or a marker related thereto in a sample from said subject" in claim 32.

19. In claim 33, the term "a threshold concentration" is vague and indefinite. It is unclear what value of "a threshold concentration" is used for comparing the concentration of MCP-1.

20. In claim 34, the term "a marker related thereto" in line 6 is vague and indefinite. It is unclear whether or not the term "a marker related thereto" in line 6 of claim 34 is referring to "a marker related thereto" in line 3 of claim 32. For the purpose of examination, the term "a marker related thereto" in line 6 of claim 34 has been interpreted as referring to "a marker related thereto" in line 3 of claim 32.

21. Claims 37-39 recite the limitation "said median thrombus precursor protein" in line 1. There is insufficient antecedent basis for this limitation in the claim.

22. Claim 40 recites the limitation "the presence or amount of one or more other subject-derived markers" in lines 1-2. There is insufficient antecedent basis for this limitation in the claim.

23. In claim 40, the term "a marker related thereto" in line 4 is vague and indefinite. It is unclear whether or not the term "a marker related thereto" in line 4 of claim 40 is referring to "a marker related thereto" in line 3 of claim 32. For the purpose of examination, the term "a marker related thereto" in line 4 of claim 40 has been interpreted as referring to "a marker related thereto" in line 3 of claim 32.

24. Claim 44 recites the limitation "the assay method" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

25. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

26. The instant claims recites "method of diagnosing atherosclerosis in a subject (p2, paragraph [0024]), comprising." According to MPEP § 2111.03, "comprising" in a method claim indicates that the claim is open-ended and allows for additional steps. Therefore, the instant claims have been interpreted as including additional steps in order to diagnose or detect presence or absence of atherosclerosis in a subject for the purpose of art rejection(s).

27. Claims 32 and 42-44 are rejected under 35 U.S.C. 102(b) as being anticipated by Parthasarathy et al. (U.S. PG Pub. No. US 2002/0052000 A1, Filed on Sept. 19, 1997).

Parthasarathy et al. teaches a method of diagnosing atherosclerosis in a subject (p2, paragraph [0024]), comprising:

- determining the presence or amount of MCP-1 in a sample from the subject (p7, paragraphs [0097] and [0098]); and
- correlating the presence or amount of MCP-1 to the presence or absence of atherosclerosis in the subject (p7, paragraphs [0097] and [0098]).

With respect to claims 42 and 43, Parthasarathy et al. teaches a method of diagnosing atherosclerosis in a subject, wherein the sample is human plasma (p2, paragraph [0024]).

With respect to claim 44, Parthasarathy et al. teaches a method of diagnosing atherosclerosis in a subject, wherein the assay method is an immunoassay method (p7, paragraph [0098]).

Claim Rejections - 35 USC § 103

28. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

29. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

30. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

31. Claim 34 is rejected under 35 U.S.C. 103(a) as being unpatentable over Parthasarathy et al. (U.S. PG Pub. No. US 2002/0052000 A1, Filed on Sept. 19, 1997) in view of Adelman et al. (U.S. Patent No. 5,482,935, Jan. 9, 1996).

Parthasarathy et al. teaches a method of diagnosing atherosclerosis in a subject as discussed above. However, Parthasarathy et al. fails to teach a method, wherein the correlating step further comprises determining the presence or amount of risk factor, wherein the risk factor is sex.

Adelman et al. teaches that several risk factor have been identified in individuals who develop atherosclerosis. It can be inferred that persons with at least one risk factor

will be at greater risk of developing atherosclerosis than persons with no risk factors. The risk factors include hyperlipidemia, hyperglycemia, diabetes, hypertension, obesity, cigarette smoking, familial hyperlipoproteinemia, aging and male sex.

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include a method of correlating the presence or amount of risk factor such as hyperlipidemia, hyperglycemia, diabetes, hypertension, obesity, cigarette smoking, familial hyperlipoproteinemia, aging and male sex to the risk of developing atherosclerosis as taught by Adelman et al. in the method of Parthasarathy et al. in order to provide additional sensitivity for the diagnosis of atherosclerosis. The advantage of determining additional information regarding high risk factors for development of atherosclerosis provides the motivation to combine teachings of Parthasarathy et al. and Adelman et al. with a reasonable expectation of success.

32. Claim 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Parthasarathy et al. (U.S. PG Pub. No. US 2002/0052000 A1, Filed on Sept. 19, 1997) in view of Carville et al. (*Clinical Chemistry*, 1996, Vol. 42, pp1537-1541).

Parthasarathy et al. teaches a method of diagnosing atherosclerosis in a subject as discussed above. However, Parthasarathy et al. fails to teach a method, further comprising determining the presence or amount of specific markers of myocardial injury.

Carville et al. teaches that acute myocardial injury (AMI) occurs by occlusive thrombosis after rupture of atherosclerotic lesions in the coronary arteries (p1537, *Introduction*, 3rd paragraph) and AMI is associated with release of cardiac muscle cell

proteins including creatine kinase (CK) and its MB isoenzyme (CKMB), troponin and myoglobin (pp1537-1538, *Introduction*, 4th paragraph). Detection of these necrotic markers form the basis of diagnostic tests for MI (pp1537-1538, *Introduction*, 4th paragraph). Further, thrombus precursor protein (TpP™) has a potential to be a beneficial aid in patient selection for early detection MI and permit more timely therapeutic intervention (pp1537-1538, *Introduction*, 4th paragraph) as TpP™ is an earlier marker of thromobosis compared to necrotic markers (CK, CKMB, troponin, and myoglobin).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to further include determining the presence or amount of specific markers of myocardial injury as taught by Carville et al. in the method of Parthasarathy et al. in order to determine risk of rupture of atherosclerotic lesions. The advantage of providing early diagnosis of atherosclerotic lesion rupture provides the motivation to combine teachings of Parthasarathy et al. and Carville et al. with a reasonable expectation of success as the early diagnosis of atherosclerotic lesion rupture has a potential to be a beneficial aid in patient selection for early detection MI and permit more timely therapeutic intervention.

Conclusion

33. No claim is allowed.

34. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Unsu Jung whose telephone number is 571-272-8506. The examiner can normally be reached on M-F: 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on 571-272-0823. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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